REMARKS/ARGUMENTS

Applicants respectfully request reconsideration of this application. By the amendments, Applicants do not acquiesce to the propriety of any of the Office's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

Information Disclosure Statement

Applicants thank the Office for its consideration of the Information Disclosure Statement mailed November 21, 2008.

According to Applicants' records, the Office has not yet considered the Information Disclosure Statement mailed on October 31, 2007. Applicants respectfully request that the Office consider this document.

In the Claims

Claims 23-26 and 40-29 are pending in this application. Claims 1-22, 27-39 and 50-54 have been previously canceled.

Claims 23 and 40 have been amended to reflect that the drug delivery composition is a dry powder. Support for the amendments to claims 23 and 40 can be found throughout the specification, for example in paragraph [0083].

No new matter has been introduced as a result of the claim amendments.

35 U.S.C. §103 Rejections

Claims 23-26 and 40-49 have been rejected under 35 USC §103(a) as being allegedly unpatentable over Milstein (US 5,693,338), in view of Laube et al. (US 5,320,094). The Office states that "it would have been obvious to one of skill in the art to combine the teachings of Milstein with Laube et al. One would have been motivated to because Laube et al. teach that the least discomforting means of administering insulin. For the foregoing reasons the instant invention would have been obvious to one of ordinary skill in the art at the time of the instant invention." (Office Action dated March 5, 2009, hereinafter "OA", page 4) Applicants respectfully disagree.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)). Furthermore, the Supreme Court in *KSR* noted that analysis supporting a rejection under 35 U.S.C. §103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at 401, 82 USPQ2d at 1396.

1. The difference between the claims and the scope of the prior art

The instant claims are drawn to a method and system for delivery of an active agent to the pulmonary system comprising dry powder microparticles of a diketopiperazine and an active agent wherein the microparticles have a diameter between 0.5 and 10 microns and the microparticles are administered in the

pharmaceutically acceptable carrier of air from a dry powder inhaler and that the active agent is released from the microparticle at a pH of 6.0 or greater. The microparticles of the present invention are administered directly to the pulmonary system as a dry powder.

Milstein teaches oral or parenteral delivery of diketopiperazine-based microparticles in tablets, capsules or liquids (column 9, lines 46-47). Milstein does not teach or suggest administration of microparticles as a dry powder directly to the pulmonary system. Milstein does not teach or suggest pulmonary administration at all, much less teach which of the numerous embodiments disclosed therein are suitable or useful for pulmonary administration.

Laube *et al.* teaches a method of delivering a protein in an aerosolized mist of small particles. Specifically, Laube teaches administration of a liquid aerosol (column 4, line 63), from a metered dose inhaler (column 3, line 40), or a nebulizer (see column 6, line 47). Laube does not teach or suggest administration of microparticles as a dry powder directly to the pulmonary system. It is not clear which, if any of the numerous embodiments disclosed in Laube are suitable or useful for pulmonary administration of dry powder.

2. The combination of the references does not teach all claim limitations

The combination of Milstein and Laube do not teach each and every limitation of the pending claims. The claims are drawn to methods of delivering an active agent to the pulmonary system as a dry powder. Milstein and Laube, individually or in combination, do not teach delivery of dry powder active agents to the pulmonary system. Nor does the combination of Milstein and Laube teach or suggest that the active agent is released from the microparticle at a pH of 6.0 or greater.

3. There is no motivation to combine the references

Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention wherein there is some teaching, suggestion,

or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 115 (Fed. Cir. 2006) MPEP §2143.01.

There is no motivation to combine the liquid aerosols and nebulizer of Laube with the microparticles taught by Milstein. Microparticles as taught by Milstein would clog Laube's nebulizer, rendering the nebulizer inoperable. "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) The microparticles of Milstein cannot be used in the system of Laube.

Conversely, there is no motivation for a person of ordinary skill in the art to start with the microparticles taught by Milstein, who does not even consider pulmonary administration, and combine them with Laube. While Laube teaches the desirability of inhalation over injection, there is no motivation to modify a system developed primarily for oral delivery, a delivery method more preferable to patients than inhalation, to achieve a pulmonary delivery system. There is no suggestion or teaching in Milstein or Laube of the need for improved methods of delivery of active agents other than those taught by Milstein and Laube. In particular, there was no suggestion or motivation to combine the teachings at the time of the invention of the subject matter of the instant claims (1995). Thus there is no motivation to combine the references.

4. Milstein and Laube do not provided one of ordinary skill in the art with a reasonable expectation of success

Laube does not provide sufficient guidance on the conditions under which microparticles are to be administered in her system. Because of this lack of guidance, it is not possible to determine the fate of the microparticles of Milstein if used in the system of Laube. Depending on the size of the microparticles and which diketopiperazine the microparticle is comprised of there are at least four possible fates for the microparticles of Milstein in the system of Laube: (1) the particles remain in suspension in the aerosol propellant and clog the nebulizer; (2) the particles remain in suspension but do not dissolve in the lung; (3) the nebulizer solution or aerosol

propellant is such that the particles dissolve prior to administration to the lung; or (4) the particles remain in suspension and dissolve upon reaching the lung tissue. There is no guidance in either Laube or Milstein as to which combination of their numerous embodiments would achieve fate (4), the claimed result of the claimed invention. Therefore, the combined references do not teach the claimed invention and there is no expectation of success to combine the references and achieve the claimed invention.

Therefore, the Office has not established *prima facie* obviousness of claims 23-26 and 40-49 over Milstein in view of Laube et al. and Applicants respectfully request the withdrawal of this rejection.

CONCLUSIONS

In light of the foregoing, Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 5 June 2009

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